The FDA's Role in Addressing the Mo99/Tc99m Shortage

Society of Nuclear Medicine and Molecular Imaging Annual Meeting

St Louis
June 9, 2014

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The opinions I express today may not necessarily reflect the official position of the Food and Drug Administration (FDA) or the Department of Health and Human Services (DHHS).

Since information on IND and NDA submissions to FDA are confidential, I need to clarify that any information in this presentation has been obtained from public sources.

Similarly, the mention of any commercial products are neither an official endorsement or criticism of the product by me, the FDA, or DHHS.

FDA working to ensure availability of Tc99m labeled drugs

- Comply with the American Medical Isotope Act of 2012 which will eliminate use of highly enriched uranium in Mo99 production.
- Work with stakeholders to rebuild fragile manufacturing infrastructure for the production of Mo99 to ensure stable drug supply.
- Work with industry to develop alternative technologies for the manufacturing of Mo99.

Tc99m is the major medical isotope in the world

- Discovered and developed in U.S. national labs
- Used in 30 million patient doses annually worldwide, including 14-15 million in the U.S. (50,000 daily)
- Represents ~80% of all nuclear medicine exams
- Ideal radionuclide
  - Optimal imaging energy (140 keV γ)
  - Practical half-life of 6 hours
  - Good chemical state
  - Easy to manufacture

Manufacturing of Tc99m

- Mo99 produced by irradiating uranium in reactor ($^{235}U + n \rightarrow$ fission products + ^{99}Mo)
- Mo99 separated from fission products
- Tc99m separated from Mo99 via column ($^{99}Mo \rightarrow {}^{99m}Tc \rightarrow {}^{99}Tc + 140\ keV\ \gamma$)

Alternative Manufacturing of Tc99m

- Mo99 can also be produced by irradiating Mo98 or Mo100 using an accelerator based process:

$^{98}Mo\ (n,\gamma)\ ^{99}Mo$

$^{100}Mo\ (\gamma,n)\ ^{99}Mo$

- Mo99 then incorporated into Generator System

(^{99}Mo -> ^{99m}Tc -> ^{99}Tc + 140 keV γ)

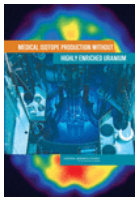
Three FDA approved products in U.S.

Mallinckrodt Ultra TechneKow ™

Lantheus TechneLite®

GE Healthcare Drytec ™

Medical Isotope Production Without Highly Enriched Uranium (HEU)



- In this 2009 report, the National Academy of Sciences (NAS) concluded that it was feasible to replace highly enriched uranium, HEU, with low enriched uranium, LEU, to produce medical isotopes and support global threat reduction.

- There was also concern that the overall process of transitioning away from HEU based production could precipitate a drug shortage. LEU, which consists of less than 20% U235, is less efficient than HEU, which consists of more than 20% U235, in producing Mo99.

The Canadian Reactors

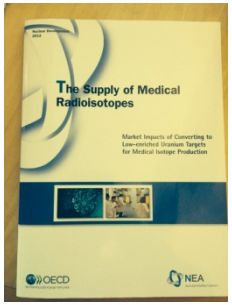
(Largest producer of Mo99)

The National Research Universal (NRU) reactor has produced as much as 67% of global Mo99. It became operational in Chalk River in 1956, and was to cease operation in 2005.

The NRU was to be replaced by the two Maple reactors, but due to design flaws these never became operational. Consequently, the NRU remained in service beyond its planned 2005 shutdown.

Shutdowns of the NRU in 2007 and 2009 precipitated several global Mo99 shortages and resulted in the establishment of the HLG-MR.

High Level Group on the Security of Supply of Medical Radioisotopes (HLG-MR)



- In 2009 the Nuclear Energy Agency of the Organization of Economic Cooperation and Development (OECD-NEA) established the HLG-MR.

- Its purpose was to come up with a plan to ensure a secure and adequate supply of Mo99 by working with 34 member governments.

FDA Responsibilities

Help prevent and mitigate drug shortages and ensure supply.

Facilitate development of new Tc99m drugs.

Approve changes in manufacturing of Tc99m drugs.

Inspect manufacturing sites.

Comply with national global threat reduction statutes and policy.

FDA Activities related to Mo99

- Drug shortage group regularly assesses current and potential drug inventory and shortages and is in contact with manufacturers.
- Provide specific advice on correct FDA regulatory pathways.
- Participate in outreach activities, e.g. participate in HLG-MR meetings, OSTP* stakeholder meetings, and Dept of Energy Isotope workshops.

*OSTP- White House Office of Science and Technology Policy

How does this apply for Mo-99?

For new drug applications (NDA) the source and production of the Mo99 needs to be specified.

For a change in manufacturing, i.e. HEU to LEU, a supplement to an approved NDA (sNDA) is filed.

Unless the protocol is spelled out within the NDA or sNDA, a drug master file (DMF) may be filed to ensure confidentiality.

This DMF specifies how the Mo99 is produced, including the composition of the target material, the irradiation process, and the chemical separation of the Mo99 from the irradiated uranium target material.

Reasons for a Drug Master File

(Small portion of an NDA)

- Maintain confidentiality of proprietary information.
- Permit efficient and review of information by reviewers at FDA to support applications submitted by more than one applicant, e.g. Company A and Company B may receive Mo99 from producer C.

Experience to date

- Several DMFs for Mo-99 production have been reviewed and accepted within one week of submission.
  - DMFs are normally reviewed only when referenced as part of an application.
  - DMFs are reviewed to determine whether they are acceptable to support a particular use, they are not approved or disapproved.
- Ultimately the review times really depend on the scope and quality of the submission.

Trend towards Non-HEU Mo99

- Currently 30 - 40% of global Mo99 is produced using Low Enriched Uranium (LEU), and is slowly increasing.

- Alternative technologies, using accelerator production of Mo99 without LEU are also in various phases of development.

The Future

Concerns

- The supply of Mo99 appears stable for 2014, but will face challenges during 2015-2020.
- In 2015, the 18 month refurbishment of the Belgium BR-2 reactor will begin,
- In 2015 French OSIRIS will shutdown permanently, to be replaced by 2020.
- In 2016, the Canadian NRU will cease Mo99 production without any replacement.

The Future

Potential new capacity

- Production capacity has been increased with the addition of Poland's MARIA and the Czech Republic's LVR-15 reactors to the reactor pool.
- Australian OPAL reactor increasing Mo99 production capacity by 2017.
- Alternative international and domestic technologies in various phases of development.
- Additional nations interested in producing Mo99 for North America.

In Conclusion

- The potential for a Mo99 shortage will continue, especially if there are multiple unplanned shutdowns, but the situation today is more stable than the past due to additional European reactors and increases in Australian capacity.

- Mo99 supply in 2015-2020 will be tight, but potential new sources, the addition of reactors to the production pool, and active coordination of reactor production schedules by the HLG-MR should make it manageable.

- FDA will continue to actively interact with the regulated industry to develop new sources, and ensure the transition to non-HEU sources of Mo99, while maintaining drug quality and purity.

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